STUDIES ON THE RATES OF RING CLOSURE OF ALPHA-OMEGA CHLOROHYDRINS WITH ALKALI HYDROXIDES

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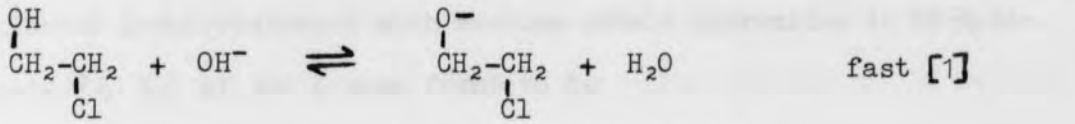
Kinetic studies were carried out to investigate a possible metallic cation effect on the rate of dehydrohalogenation of alpha-omega chlorohydrins. The rate constants obtained for 2-chloroethanol with alkali hydroxides in 62.5 % dioxane—37.5 % H_2O at 0° C did not reveal a significant effect although the trend proceeded in the expected direction. While testing for more favorable reaction conditions it was found that the order of ease of reaction for 2-chloroethanol in several aprotic solvents is DMSO > Dioxane > THF > DMF. The order of the rate of ring closure as a function of ring size was investigated and found to be 3 > 5 > 4 > 7.

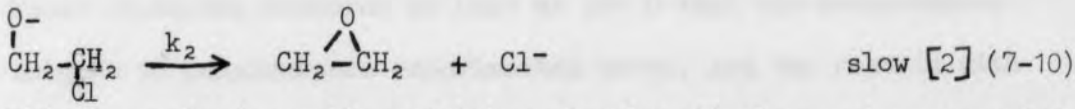
Only recently has attention been centered on the fact that a cation effect exists in certain types of organic reactions involving alkali bases. Due to the increasing ionic character with increasing atomic weight of the alkali cation in such reagents, the order of reactivity of the alkali reagent in a reaction dependent upon ionic activity would ordinarily be $(CH_3)_4N^+ > Cs^+ > K^+ > Na^+ > Li^+$. However, in some reaction mechanisms, coordination of the alkali cation with an electron pair on an organic functional group becomes an important factor in the reaction kinetics involved. In this respect, the lithium ion should possess the greatest coordinating ability among the alkali cations due to its small size and greater coordinating ability. A number of studies in recent years have demonstrated the existence of such cation effects in reactions involving strong alkali bases (1-5).

The purpose of this project was to confirm and extend recent studies (6) on the alkali metal cation effect in chlorohydrin ring closure reactions.

Initial studies were made to determine the alkali cation effect on the rate of dehydrohalogenation of ethylene chlorohydrin to form ethylene oxide. The kinetics of the reaction between ethylene chlorohydrin and various alkali metal hydroxides were investigated. That the reaction involved an intermediate alkoxide anion in the stepwise mechanism had been proven in earlier studies by Swain and co-workers (7).



fast [1]



slow [2] (7-10)

This is an Sn i reaction of intramolecular displacement accompanied by complete inversion at the carbon attached to the halide. The rate equations are as follows:

$$\frac{d[Cl^-]}{d\,t} = k_2[CH_2ClCH_2O^-] = k_2K_1[CH_2OHCH_2Cl]\ [OH^-]$$

where K_1 is the equilibrium constant for equation [1] (10). The second order rate constant, $k = k_2K_1$. Two factors are of primary importance in determining k, the acidity of the alcoholic hydrogen, and the ease of elimination of the halogen. Swain compared the rate of hydrolysis of 2-chloroethanol in light and heavy water, and found the rate 54 % greater in heavy water than in light. This demonstrated that the loss of the alcoholic hydrogen proceeds prior to the rate determining step in equation [2]. If this had not been the case, there would have been no isotope effect found or possibly the reaction would have proceeded faster in light water (7).

Since it was observed that the slow step is involved with the reactivity of the intermediate alkoxide anion, which should be associated

with the metallic cation during the reaction, it seemed possible that one might observe a cation effect in this reaction. The smaller the degree of association occurring, the more rapid should be the displacement of the chloride ion. From this reasoning it was proposed that the order of reactivity among the alkali cations studied would be $(CH_3)_4N^+ > Cs^+ > K^+ > Na^+ > Li^+$. Rate constants (x 10^{+2}) previously obtained for the reaction of 2-chloroethanol with various alkali hydroxides in 88 % dioxane-12 % H_2O at 25° C were found to be

$(CH_3)_4N^+$, 8.7; Li^+, 3.8; Na^+, K^+, Cs^+, 2.4 (6)

These reactions occurred so fast at 25° C that the measurements were subject to considerable experimental error, and the results with lithium seemed out of line. Therefore, it was decided to repeat these experiments at a lower temperature in order to obtain slower rates which would be less subject to error in measurements. The technique of following the rate was improved by using a combination of pH measurement and indicator to monitor the titrations for unreacted alkali, whereas only the indicator had been used in the earlier study.

Results obtained at 0° C are given in Table 1.

TABLE 1

Second Order Rate Constants for the Reaction of 2-Chloroethanol with Alkali Hydroxides in 62.5 % Dioxane-37.5 % Water at 0° C.

Cation	Nbase	M(2-chloroethanol)	k x 10^3	Deviation
Li^+	0.0314	0.0701	4.5	± 0.4
Na^+	0.0346	0.0701	4.9	± 0.9
K^+	0.0318	0.0701	6.6	± 0.6
Cs^+	0.0329	0.0701	4.9	± 0.6
$(CH_3)_4N^+$ (11)	0.0333	0.0701	6.1	± 0.9

Since it was necessary to use a higher percentage of water in the solvent medium when operating at 0° C in order to maintain a homogeneous system, these measurements were made in 62.5 % Dioxane-37.5 % water, which was the highest percentage of dioxane that could be used without encountering partial freezing out of the solutions. While these results appear to conform, in general, to the expected trend of reactivity, they are not in agreement with those obtained previously in 88 % dioxane-12 % water. It has been shown that as the water content of the solvent mixture is increased, the cation effect decreases (12). This might be expected because the alkoxide ion may be preferentially solvated by water molecules thus diminishing the cation effect.

Tests were then begun to find an aprotic solvent which might bring out a cation effect by allowing higher percentages of organic solvent to be employed. The findings are summarized in Table 2.

TABLE 2

Second Order Rate Constants for the Reaction of 2-Chloroethanol with Sodium Hydroxide in 62.5 % Aprotic Solvent and 37.5 % Water.

Solvent	M(2-Chloroethanol)	N_{NaOH}	T(°C)	t(min)	k(1/n-sec)
Dioxane	0.080	0.042	25	30	0.70
Dioxane	0.070	0.031	0	60	4.9×10^{-3}
THF	0.080	0.030	25	60	2.2×10^{-3}
DMF	0.080	0.033	25	60	6.4×10^{-4}
DMSO	0.079	0.039	0	15	2.9

The order of reaction rate in the solvents was found to be dimethyl sulfoxide (DMSO) > p-dioxane > tetrahydrofuran (THF) > N,N-dimethylformamide (DMF). The values for the dielectric constants of these solvents are 48.9^{20} (13), 2.2^{25} (14), 7.3^{25} (15), 36.7^{25} (16), respectively,

and for H_2O, 78.5^{25} (14). Early work (17), (18) on this system has suggested that a decrease in dielectric constant brings about an increase in the second order reaction rate. More recent studies have shown this relationship to be linear, except in cases where solution phenomena interfere. At 25° C acetone and dioxane mixtures deviate slightly from linearity below 12 % dioxane but the acetone-THF system conforms (19). Dioxane has been shown to lower the dielectric constant of water much more than predicted by theory, exhibiting a solution phenomenon(20). Thus, the rates of the reaction in dioxane, THF, and DMF appear to be explained by the relationships of their dielectric constants. The DMSO appears to have a pronounced solution intereaction because the rate of the displacement reaction is much out of line with its high dielectric constant. This greater reactivity in DMSO as compared to solvents of lower dielectric constant such as DMF has been previously established in kinetic studies of reactions for preparation of nitriles (21) and aromatic fluorine compounds (22).

Several pilot studies using only NaOH as the base at 25° C were made with chlorohydrins other than 2-chloroethanol to find a system which might lend itself more readily to kinetic studies for the different alkali metal ions and to determine the effect of ring size upon the rate of ring closure. The results appear in Table 3.

TABLE 3

Second Order Rates of Various Chlorohydrins with Sodium Hydroxide in 62.5 % Dioxane and 37.5 % Water.

Chlorohydrin	Ring Size	M (chlorohydrin)	N NaOH	T °C	t min.	k (1/n-sec)
2-chloroethanol	3	0.070	0.031	0	60	4.9×10^{-3}
2-chloroethanol	3	0.080	0.042	25	30	0.7
3-chloropropanol	4	0.090	0.040	25	60	too slow to be significant
4-chlorobutanol	5	0.080	0.042	25	60	8.1×10^{-3}
6-chlorohexanol	7	0.08	0.03	25	60	too slow to be significant
3-chloropropanol	4	0.090	0.040	87.5*	60	42 % base used
6-chlorohexanol	7	0.80**	0.50	90.0*	60	19 % base used

*reflux conditions

** 50 % dioxane had to be used because more concentrated base formed two phases in the 62.5 % dioxane system.

The rates of ring closure are in general agreement with those theoretically proposed. Thus, the five-membered ring, which is more thermodynamically stable than the four because the bond angles are not strained far from the preferred tetrahedral angle, forms much faster than the latter. However, the extremely rapid rate of closure of the three-membered ring seems at first surprising in view of the well known thermodynamic instability of the strained 60° C-C bonds. Apparently, in this case, the favorable entropy factor, due to the limited number of conformations available, is more than enough to compensate for the unfavorable thermodynamic factor.

The statistical probability of two ends of the alkoxide anion of 6-chlorohexanol coming within the range of interaction is much lower than

that of the other chlorohydrins used, due to its greater chain length. Thus this system was the slowest studied.

The 4-chlorobutanol system appears to be more favorable than the 2-chloroethanol for kinetic studies at 25° C. The reaction proceeds more slowly so that higher concentrations of reactants might be tried to improve the accuracy of the results. Even more important, this ring closure appears to proceed slowly enough so that it would be feasible to study the reaction at 25° C. At this temperature it would be possible to work in high (88 %) concentrations of dioxane and minimize the obscuring of the cation effect encountered when higher proportions of water have to be used (see p. 3).

The relatively slow rates of closure observed with 2-chloroethanol when THF and DMF were employed (see Table 2) likewise suggest that these may be better solvents to use for comparison of cation effects than dioxane-H_2O.

It would also be of interest to make pilot runs on 5-chloropentanol for comparison with other ring sizes. One might predict that the relative rates of closure with this compound, which would yield a six-membered ring, would be somewhat slower than that leading to a five-membered ring and perhaps even more favorable for a kinetic study.

Studies of the kinetics with an added salt may also prove valuable, particularly if one were to employ a strongly coordinating cation, such as Li^+, as the added salt (e.g., $LiNO_3$). One might possibly find an increase in rate with such added salts if the cation would coordinate enough with the chloride ion to exert a "pull" effect to aid in the main displacement attack by the neighboring alkoxide anion. Previous workers (9) have shown added salts to have negligible or slightly negative effects on

the rates of ring closure of 2-chloroethanol, but these studies used only the weakly coordinating Na and K cations in relatively dilute aqueous solutions where water solvation would likely mask any cation effect.

EXPERIMENTAL

The best grade of Matheson, Coleman and Bell's 2-chloroethanol, 3-chloropropanol, and 6-chlorohexanol were used. The technical grade of 4-chlorobutanol had to be used since higher grade material was not commercially available. Each was purified by preliminary drying over Drierite followed by distillation at reduced pressure. The 2-chloroethanol was collected at 60 mm Hg over a temperature range of 63.0-64.0° C (23). 3-Chloropropanol* was distilled at 40.0-41.0° C; 4-chlorobutanol, at 10 mm pressure and 72.5-74.0° C; and 6-chlorohexanol* at 84-85° C. An Aerograph 600-D vapor phase chromatograph, a Beckman IR-5A, and an accumelt apparatus (American Instrument Co., Inc.) were used to determine the degree of purity of these redistilled products. The 2-chloroethanol was quite pure. The 6-chlorohexanol had only a slight impurity, while the 3-chloropropanol and 4-chlorobutanol contained a bit more contamination which was not considered significant, however, because the runs were pilot studies.

The chlorohydrin solutions were prepared by accurately weighing the required amount of chlorohydrin and diluting** to final volume with

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*The pressure of the 3-chloropropanol and 6-chlorohexanol distillations did not correspond to literature data due to a malfunction of the pressure gauge. The temperature range of collection indicates a fair degree of purity.

**Chlorohydrin solutions were initially prepared in 100 % p-dioxane (the first solvent used) to obtain reaction solution of 87.5 % in dioxane. At this concentration the solution freezes above 0° C. An alteration was made to obtain a mixture of a lower freezing point (24).

1:1 water-aprotic solvent when the reaction mixture was 62.5 % solvent.

The solvents used in conjunction with water in preparing the reaction solutions were p-dioxane, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), and tetrahydrofuran (THF).

The p-dioxane was purified by refluxing with concentrated hydrochloric acid under a stream of helium preceded by preliminary drying with potassium hydroxide and distillation from metallic sodium. It was protected from air by flushing with helium. The DMSO was distilled at 25 mm pressure from CaH_2 and collected at 87-89° C. The THF was dried over KOH and distilled from CaH_2 at 83-85° C/20-22 mm. The DMF was not purified by distillation but the pH was checked and found to be neutral.

The standard bases were prepared by dilution of initial stock solutions so that the resulting solutions were 1:3 water-aprotic solvent.* Each stock solution was carefully made using boiled, de-ionized water to insure a carbonate free solution. Gooch crucibles were employed for preparing the stock NaOH and KOH solutions. CsOH was prepared from CsCl by the method of C. H. Vanselow, wherein an aqueous solution of CsCl is stirred for four hours with a 25 % excess of thoroughly washed silver oxide precipitate, followed by filtering off the precipitated silver chloride and excess silver oxide, and standardization of the filtrate. The 25 % TMA in aqueous solution was the best grade of Matheson, Coleman and Bell. Periodical checks by titrations were made on the diluted base solutions when kept over prolonged lengths of time. All the base solutions

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*When a 0.08 N LiOH solution was prepared in 75 % DMSO a white, particulate precipitate formed which was soluble in water, did not give a carbonate test with acid, and was found to be basic when dissolved in water and titrated with hydrochloric acid. No other base used gave this reaction with DMSO.

were stored in a CO_2 free closet in tightly capped polyethylene bottles. The standard hydrochloric acid was prepared from analytical grade reagent and standardized with potassium acid phthalate.

Kinetic runs were performed at 0° C in Dewar flasks by using a slurry of ice and water as the coolant. The reactants were separately cooled at 0° C before mixing. At intervals, 10 ml aliquots were withdrawn, diluted with 100 ml of H_2O at 0° C, and titrated. Times were recorded when pipettes were half empty.

The kinetic runs at 25° C were carried out in a constant temperature bath which maintained temperatures to ± 0.5° C. The same sampling procedure was used.

During the titration, the solution was constantly stirred with a magnetic stirrer. A Beckman Zeromatic II pH meter and a Sargent combination micro electrode were used in conjunction with bromthymol blue (25) to determine the end point of the titration at a pH of 7.

All runs in a particular series of base concentrations were carried out during the shortest length of time possible, usually in one day, to insure uniformity.

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